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Review Article

Advancements In the Treatment of Diabetic Neuropathy: A Comprehensive Review of Formulations and Characterization Studies

Rida Sayed, Aamina Shaikh, Sadiya Sabahat, Mantasha Sayyed, Rummanah Firdowsi, Tahsin Attar*

Anjuman-I-Islam's Kalsekar Technical Campus – SOP, New Panvel, Navi Mumbai, Maharashtra, India.

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ABSTRACT

Diabetic neuropathy is a severe consequence of diabetes that affects peripheral nerves and causes issues that include numbness, pain, and weakness, greatly decreasing quality of life. The condition's complexity has necessitated the development of more efficient therapeutic approaches that go beyond traditional treatments. This review looks at recent advances in novel medicine delivery technologies for diabetic neuropathy. These innovative formulations are designed to enhance the bio-availability, stability, and targeted, sustained release of therapeutic agents. In preclinical studies, the use of natural bio active chemicals and innovative nanotechnology-based delivery methods yielded promising findings, with prospective improvements in pain treatment, nerve healing, and neuroprotection. By investigating these breakthroughs, this review article highlights the promise of these novel approaches in treating diabetic neuropathy for more efficient therapeutic outcomes.

INTRODUCTION

Diabetes mellitus is a syndrome arising from hyperglycaemic conditions that decrease insulin level and its action to maintain the glycaemic balance. Insulin, it is a hormone that helps our bodies to use energy from food. When there is not enough insulin, or when our body does not respond

well, it can cause problems with the breakdown of carbohydrates, fats, and proteins. This can lead to health issues like diabetes. Many people with type 2 diabetes don't have any symptoms, especially in the early stages. But humans with high blood sugar, especially children, might experience excessive thirst, urination, hunger, weight loss,

*Corresponding Author: Tahsin Attar

Address: Anjuman-I-Islam's Kalsekar Technical Campus – SOP, New Panvel, Navi Mumbai, Maharashtra, India.

Email ✉: tahsin.attar@aiktc.ac.in

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and blurry vision. If diabetes isn't treated properly, it can cause serious problems like confusion, unconsciousness, and even death. This is often caused by a buildup of acids in blood or other complications. There are two forms of Diabetes, type 1 & type 2. Type 1 diabetes arises when the immune system mistakenly attacks and destroys the insulin-producing cells in the pancreas. This damage is brought about by both T cells and B cells. In patients with type 2 diabetes, targeted insulin resistance leads to an increased requirement of the hormone by insulin-target tissues. But with the increased demand for insulin over time due to slow destruction of β cells, insulin secretion decreases in some type 2 diabetes patients can be changed from independence to dependence on Insulin. [1] For instance, in one category of diabetes (type 1), A group of patients with this kind of diabetes (about a third) may be identified by the presence in serum samples from all newly diagnosed diabetic subjects, before treatment is started to determine whether they have immune markers. And/or genetic, which shows a chronic destruction process in their insulin-producing cells. Type 2 diabetes is far more ordinary than type 1 disease- is characterized by opposition to insulin action plus inadequate compensatory increase in the secretion of this hormone. A type of asymptomatic hyperglycaemia can resist for years before diabetes is diagnosed because its severity reaches levels high enough to usher in pathologic and functional changes on various target tissues. Carbohydrate metabolism can be investigated by examining the level of plasma glucose in fasting conditions or following an oral glucose load despite this period being asymptomatic. [7] Diabetes also classified as gestational diabetes, is any degree of diabetes or glucose intolerance that is identified in the early pregnancy, generally in the second or third trimester. The most recent guidelines from the International Association of the Diabetes and

Pregnancy Study Groups, however, do not include diabetes that is diagnosed during or after pregnancy in high-risk women, such as whoever is obese, where any degree of glucose intolerance is classified as overt diabetes rather than previously diagnosed GDM. In contrast to any underlying diabetes in pregnant women's, gestational diabetes mellitus (GDM) typically goes away quickly upon delivery or pregnancy termination. [8] Glycolysis is an enzyme-catalysed metabolic process that encourages cells to break down glucose and produce pyruvate. During a fast, the cytosol and mitochondria of hepatocytes engage in several metabolic processes that synthesize glucose from non-carbohydrate substrates to maintain stable blood sugar and glucose levels. It is regulated by cortisol, glucagon, and insulin. Moreover, the initiation of glycogenolysis is triggered by the pancreas' production of glucagon during fasting. Glycogen is broken down biologically in a process known as glycogenolysis to create glucose and glucose-1-phosphate. Glycogenesis is the process of synthesizing glycogen, and glucose molecules link the glycogen linkages for storage. The controlled process of glucose transport involves the employ of carrier proteins to enable diffusion across cell membranes. Although there are different other varieties of glucose transporters, GLUT1–5 glucose transporters are the utmost significant. Stress-related variables including hormones, toxins, kinase signalling, and inflammation can modify the shape, expression, distribution, synthesis, and activities of transport proteins which are engaged in glucose transport. Certain changes in glucose transport promote or worsen conditions like diabetes. [9]

Diabetic neuropathy is an obstacle of diabetes mellitus. Diabetic peripheral neuropathy happens when people with diabetes experience nerve problems in their hands or feet. When it causes loss of sensation because of nerve dysfunction. Symptoms arise after many years which cause



damage to the quality of life of a patient. [2] The pathophysiology of diabetic peripheral neuropathy involves a condition where nerves in the body become damaged. This damage can cause pain, numbness, and loss of feeling. The nerves are damaged in a way that affects all types of nerve fibres and gets worse from the centre of the body outward. [3] Diabetic neuropathic pain feels like tingling, sharp, burning shooting, or even electric shock sensations. Diabetic neuropathic pain can be quite severe, especially at night, and can disrupt sleep. It can be constant and sometimes makes even light touches feel painful. This can significantly impact a person's quality of life, making it difficult to do daily activities and affecting their mood. The pain may also lead to avoiding social activities and can be linked to depression. Scientists aren't completely sure what causes diabetic neuropathic pain. There are different ideas, like changes in blood flow to the nerves, problems with metabolism and the immune system, changes in nerve signals, and problems in the brain. Some things that can grow the risk of diabetic neuropathic pain include high blood sugar levels, being older, having diabetes for a long time, drinking alcohol, and smoking. Even though we know a lot about how diabetes can cause problems, we don't understand why few people with diabetes have painful nerve problems while others don't. Scientists are trying to determine why nerve damage happens and how it leads to pain and other problems. But, interestingly, the amount of pain doesn't always match the amount of nerve damage, and sometimes people can have pain even without nerve damage. [4] This primer focuses on distal symmetric polyneuropathy, the most prevalent type of diabetic neuropathy; henceforth, it will be referred to as diabetic neuropathy. Distal symmetric polyneuropathy typically affects the hands and lower limbs, with a "stocking and glove" distribution. The constellation of

autonomic neuropathies, such as cardiac autonomic neuropathy, gastrointestinal dysmotility, diabetic cytopathy, and impotence, are among the several diffuse neuropathies that can result from diabetes. Less frequently, focal neuropathies include peripheral nerve illness that results in isolated mononeuropathies or, less frequently, nerve root dysfunction that results in radiculopathy or polyradiculopathy. [10]

Individuals with diabetic neuropathy may have heart attacks without realizing it. This can shorten their lifespan, with 25% to 50% of them dying within 5 to 10 years. Two-thirds of diabetes people are thought to have either subclinical or symptomatic neuropathy. Quantitative sensory and autonomic tests as well as electrodiagnostic testing are necessary for the recognition of subclinical DN. Neuropathy can occur in patients with diabetes of different kind, involving those with insulin-dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), and secondary diabetic patients. [5] Older adults are more likely to die from high blood sugar problems. They're also twice as likely to go to the emergency room for low blood sugar compared to other people with diabetes. Nerve damage is common in older people with diabetes. This damage can impact different types of nerves and can cause numbness or loss of feeling in the feet. [6] According to WHO the number of people with diabetic neuropathy has more than tripled since 1990. It has risen up to 206 million in 2021. [15] The diabetes mortality rate increased 3% by age from 2000 to 2019. [16]

**MATERIALS AND METHODS:
DIFFERENT FORMULATIONS THAT
SHOWED POSITIVE EFFECT IN
TREATMENT OF DIABETIC
NEUROPATHY AND THEIR
CHARACTERIZATION STUDIES.**



1. SNEDDS (SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM) CURCUMIN FORMULATION METHOD

1.1 Drugs and Chemicals:

Curcumin was acquired from India's Hi Media Laboratories. Sigma-Aldrich in the United States was the source of streptozotocin (STZ). An Accurex kit for glucose oxidase-peroxidase (GODPOD) was acquired from India. Tetrahydrofuran and acetonitrile were acquired from J.T. Baker in the United States. India's Merck Limited supplied the citric acid and polyethylene glycol (PEG 400). Gift samples of Labrasol and Gelucire® 44/14 were provided by Gattafosse Pvt. Ltd., located in Saint Priest, France. Eurochem Asia was the supplier of Vit. E TPGS. [11]

1.2 SNEDDS formulation of curcumin:

Qualitative Formula:

SNEDDS included Gelucire 44/14, Labrasol, Vitamin E, NTPGS, PEG 400, citric acid anhydrous, ethanol, and HPMC E5. Every milliliter of SNEDDS had 66.7 milligrams of curcumin. [11]

Preparation of SNEDDS:

Gelucire 44/14, Vit. E TPGS, Labrasol, and PEG 400 were added to a vial, heated to 60°C, and thoroughly mixed. Citric acid predissolved in ethanol was added to the mixture. Curcumin was dissolved in this mixture by vortexing for 30 minutes, and then HPMC E5 was added. [11]

1.3 Characterization of SNEDDS Curcumin Formulation:

Globule Size Analysis:

SNEDDS was diluted 250 times (from 40 µl to 10 ml) in distilled water filtered via a 0.2 µM filter. To analyze the globule size and distribution in the SNEDDS formulation, the sample was diluted and measured using dynamic light scattering (DLS) (Nano ZS, Malvern, UK) and the Cumulants analysis method, with the average of five measurements. Further, the mass average globule

size was estimated using the method reported by Zhu et al. [11]

Transmission Electron Microscopy (TEM):

The SNEDDS formulation was diluted with distilled water (250 times), filtered through a 0.45 µM filter, and combined with gentle shaking. One drop of diluted sample was placed on a carbon-coated copper grid, allowing for examination of globule morphology at room temperature using a transmission electron microscope (Hitachi H-7500, Japan). The samples were examined without any dye staining. To produce the contrast, samples were studied using a lower accelerating voltage of 80 kV and a narrower objective aperture. Images were taken at 15000× magnification. [11]

2. PHYTOCONSTITUENT BASED FORMULATION FOR DIABETIC NEUROPATHY

2.1 Material and Methods

Identification, Collection and Plant Material Authentication:

Samples of *Morus Alba* stem bark were collected by the IFTM Institute Botanic Garden in Moradabad, India, in January. The bark was washed and allowed to air dry. The Chief Scientist, RHMD, CSIR-NIScPR, Delhi, India, authenticated the data. A sample of the voucher was sent to the division for further processing. [12]

Drugs and Chemicals:

Chemicals were sourced from Central medication House Ltd., New Delhi, India, and Metformin, the reference medication (purity: 99.9%), was provided by CDH (P) Ltd., Delhi, India. [12]

Extraction:

The stem bark was gathered, rinsed with running water, and air-dried over a period of two to three weeks. The yellowish layer beneath was exposed by lightly scratching the fully dried stem. The stem bark or cortex was removed with a knife, sliced into small pieces, and blended until powdered. Sieving the raw powder produced a fine, homogenous powder. Before being shaken, M.



Alba stem bark powder was soaked in 75% ethanol for ten days. The extract has been filtered. Fresh ethanol was used to extract the residue once more to ensure full extraction. The filtrates were sieved and air-dried to a powder before being tested at 4°C. [12]

Isolation:

The extract was subjected to silica gel column chromatography (Merck Silica gel 60/0.0630.200 mm). The column was filled with a 3:7 solvent solution of n-hexane and ethyl acetate. There were three sub-fractions found: A, B, and C. A molecule with an estimated R_f value of 0.76 was identified from subtraction B (n-hexane-ethyl acetate; 3:7). Then it was concentrated and 99 mg were obtained. The extraction process was repeated multiple times to obtain enough isolated chemical for the testing. NMR, FTIR, and mass spectroscopy were used to complete the characterization process. [12]

Development of oil-in-water Nanoemulsions:

The formulations shown were employed to create a phytoconstituent-loaded oil-in-water nanoemulsion. The oil phase consisted of sorbitan monooleate (Span 80; 1-2.5% w/w), ethanol (7.5% w/w), and coconut oil (7.5% w/w). The aqueous phase is composed of water (80–83%) and polysorbate 20 (Tween 20; 1-2.5% w/w). To form an emulsion, the water and oil phases were heated to 60 degrees Celsius while swirling. The two phases were combined and homogenized for three minutes at 10,000 rpm. Lastly, the chrysin-Nanoemulsion was produced by passing the pre-emulsion via a microfluidizer. The distribution of particle sizes, average particle size, and surface charge of phytoconstituent-NE nanocolloids were then investigated. [12]

2.2 Characterization of Nanoemulsion:

Physical Parameters:

Physical factors such as color, odor, and storage conditions were determined for the generated nanoemulsions. [12]

Measurement of pH:

A 30 ml sample was placed in 50 ml beakers to measure the pH of all generated NEs with a pH meter (Ali and Hussein 2017). Each measurement was performed three times. [12]

Determination of Refractive Index:

The nanoemulsion's refractive index was determined using an Abbes refractometer at $25 \pm 0.5^\circ$. A drop of the formulation was put on a slide and compared to the refractive index of water, which is 1.333. If a nanoemulsion's refractive index equals that of water, it is termed transparent. [12]

Determination of Viscosity:

The viscosity measurement is an important aspect in the physicochemical characterisation of nanoemulsions. A viscometer was used to measure the viscosity of a nanoemulsion. [12]

Determination of Surface Tension:

Surface tension was measured using a stalagmometer, employing the drop count method. [12]

Determination of Zeta Potential:

The measurement was conducted using a Malvern Zeta Sizer device. The zeta potential, derived from the electrophoretic mobility of the oil droplets, was assessed by diluting the nanoemulsion. [12]

FESEM Examination:

The image was created step-by-step by scanning a focussed electron beam across the material with the FESEM JSM 6100 for evaluation. Several elastic scattering processes deflected the source electrons after they had entered the solid material. The incident electrons produced a multitude of signals, which were subsequently combined to form an image or inspect the sample surface. [12]

Stability Study:

The physical stability of the nanoemulsion formulations was evaluated by storing them at -18°C in the refrigerator for three months, 75% relative humidity (RH), and 40°C in an oven. After one to three months of storage, the NE



qualities include zeta potential, refractive index, viscosity, pH, and surface tension. [12]

3. PHYTOPHOSPHOLIPID NANOVESICULAR SYSTEMS FOR DIABETIC NEUROPATHY TREATMENT

3.1 Materials and Methods:

Curcuma longa and Boswellia serrata were purchased from a local reputable herbal distributor in Kanpur, Uttar Pradesh, recognized at Pranveer Singh Institute of Technology in Kanpur, and phytochemically tested using spectrophotometry. Changshuyangyuan Chemical China/Central Pharmaceutical House, New Delhi, supplied methanol, ethanol, and triethanolamine. SD Fine Chemicals Limited in Mumbai supplied methyl paraben, pet ether, vanillin, and toluene. SD Fine Chemicals Limited of Mumbai delivered carbopol 934, soy lecithin, and propylene glycol. [13]

Extraction of Herbs:

It is the procedure used to isolate a particular element from a mixture or raw material. To extract chemical components for our experiment, we used Curcuma longa and Boswellia serrata. [13]

Curcuma longa Extraction:

Curcuma longa dried roots were purchased from a local Kanpur shop. After passing through filter #60, the roots had been crushed and the appropriate particle size was obtained. The soxhlet apparatus was used to do solvent extraction using pet-ether as the solvent. Rotavapour was employed for eliminating the solvent following extraction. The finished oil should be wrapped in aluminum foil and stored in a glass jar in the refrigerator at 9-10°C until used. [13]

Boswellia serrata Extraction:

The Boswellia serrata oleo gum resin was purchased from the official India Mart website. The plant's oleogum resin was combined with hot distilled water on a magnetic heater for 1.5 hours before the extract was filtered. Rotavapour was employed to eliminate the solvent. The porous

powder that formed was stored in the refrigerator at 4-8°C until needed. [13]

Thin Layer Chromatography (TLC):

It is a chromatographic technique for separating non-volatile compounds in a mixture. TLC plates were made with silica gel GF 250 to validate a process of synthetics and identify the result. A silica gel slurry was prepared using distilled water and then placed on TLC glass plates before being baked for 30 minutes at 30 degrees Celsius. UV and iodine chambers were employed for visualization. [13]

Partition Coefficient of Extracts:

10 mL N octanol and 10 mL phosphate buffer pH 6.8 were mixed in a separate funnel for 60 minutes. Curcuma longa and Boswellia serrata extracts (1 mL each) were incorporated to the mixture and stirred for 30 minutes. After separating the organic and aqueous layers, the partition coefficient was determined employing a UV visible spectrophotometer. [13]

UV Spectrophotometer Study:

Stock solutions of Curcuma longa and Boswellia serrata were prepared in phosphate buffer pH 6.8 at 1000 µg/ml concentrations. UV spectrophotometry was employed for scanning the wavelength spectrum of 200-400 nm at concentrations ranging from 2-10 µg/ml of the stock solution. Then, varied concentrations of Curcuma longa and Boswellia serrata were exposed to UV to determine absorbance at the scanned maximum. [13]

Method of Preparation of Ethosomes:

The cold technique was utilized to create polyherbal ethosomes. Phospholipid and lipophilic herbal extracts were combined in ethanol at room temperature with a mixer and vigorous shake. During the stirring, 5 mL of propylene glycol was introduced. The mixture of ingredients has been heated in a water bath to 30°C±1°C and constantly mixed at 700 rpm using a mechanical stirrer. In a separate jar, the



hydrophilic extract was heated to $30^{\circ}\text{C}\pm 1^{\circ}\text{C}$ with water. One drop at a time, the aqueous phase was added to the non-aqueous phase in a covered beaker, and the mixture was mixed for five minutes. The formulation was cooled at room temperature for 30 minutes before being sonicated at 40°C for five three-minute cycles with a one-minute break between cycles to reach the desired ethosome size. The entire formulation was then kept in the refrigerator. [13]

Formulation of Ethosomal Gel:

To improve ethosomal suspensions, studies with zeta potential, trapping efficiency, and release were conducted. Carbopol 934 was used to turn optimal ethosomal suspensions (Ne8 and Ne9) into gel. Carbopol 934 expanded overnight after being circulated in distilled water at 300 rpm for two hours. After one day, increased ethosomal suspensions were added to carbopol dropwise while being constantly stirred to form a homogenous mixture. Triethanolamine was introduced until a clear gel was formed. 0.01 percent benzalkonium chloride was employed as a preservative to prevent bacteria and fungal growth. [13]

3.2 Characterization of Ethosomes:

Scanning Electron Microscopy (SEM):

SEM provides details on the sample's morphology and focuses on the sample's surface and composition. SEM may also provide three-dimensional images. Jeol examined the surface appearance of manufactured ethosomes using a scanning electron microscope model JSM6490LV from Babasahab Bhimrao Ambedkar University in Lucknow. [13]

Fourier-Transform Infrared Spectroscopy (FTIR):

Infrared spectroscopy analysis reveals the existence of any functional groups in an unidentified molecule. In this study, we identified functional groups using a Perkin Elmer FTIR

spectrometer. All formulations were tested within the 4000-400 cm^{-1} wavelength range. [13]

Zeta Potential:

Because it is an important indicator of particle surface charge, it is used to identify and regulate the stability of suspension particles. The negative zeta potentials of the ethosomes ranged from -11.4 mV to -29.6 mV. The largest negative zeta potential was found in the optimised formulation NE8, which was thought to be advantageous for formulation stability and drug transdermal permeation improvement due to electrostatic repulsion between skin surfaces of the same charge, claiming that the formulated ethosomes do not aggregate rapidly. The charge of vesicles is an important component influencing both stability and interactivity of skin vesicles. [13]

Drying Rate of Ethosomal Gel:

Drying studies were conducted in a vacuum tray drier where the temperature and vacuum could be controlled separately. An exact quantity of ethosomal gel was put in a petridish and maintained in an oven at $50\text{-}60^{\circ}\text{C}$. The sample weight was measured and recorded at 10-minute intervals. The drying qualities were evaluated using data on moisture lost over time. [13]

4. TRANSDERMAL DELIVERY OF CAPSAICIN NANOEMULGEL: OPTIMIZATION, SKIN PERMEATION AND IN VIVO ACTIVITY AGAINST DIABETIC NEUROPATHY

4.1 Materials and Methods:

Capsaicin, eucalyptus oil, carbopol 940, triethanolamine, McCoy 5A medium, and alloxan were all acquired from Sigma-Aldrich, USA. Fluka in Germany provided ethanol ($\geq 99.5\%$), isopropyl alcohol ($\geq 99.7\%$), propylene glycol, and Tween 80. [14]

Formulation of nanoemulgel:

The nanoemulgel was formed by mixing the prescribed nanoemulsion with the gel base. The gel was created following Harwansh et al's



approach, with slight changes. To make the 1% gel, 1 g of Carbopol 940 was distributed in 100 mL of deionised water and allowed to swell for a day at room temperature. After complete swelling, 10 g of propylene glycol and isopropyl alcohol were added and mixed with a magnetic stirrer. The generated gel was then gently and evenly added to the nanoemulsion while stirring (100 rpm). Finally, a few drops of triethanolamine were added and mixed to create an emulgel with a neutral pH. [14]

4.2 Characterization Studies:

Droplet size and polydispersity index :

The mean droplet size and polydispersity index of nanoemulsions were measured using a Zetasizer (Malvern Zetasizer Nano-ZS90, Worcestershire, UK). All measurements were taken at a 90-degree angle and 25°C. [14]

Transmission electron microscope (TEM) :

The morphology of the optimised formulation was investigated using a Morgagni 268D transmission electron microscope (FEI Company, the Netherlands). Samples were placed on a carbon-coated grid and treated with 1 drop of 2% phosphotungstic acid. The treated sample was then air-dried and covered in a slip before being examined under TEM. [14]

Viscosity and conductivity of the nanoemulsion:

The viscosity of the nanoemulsion was determined undiluted using a Brookfield viscometer (DVII + Pro Viscometer, Bohlin Visco 88, Malvern, UK), with samples (30 mL) equilibrated for 5 minutes prior to measurement.[14] Electrical conductivity was measured at room temperature using an EC tester II (USA). All measurements were collected in triplicate. [14]

Stability study of capsaicin nanoemulsion:

Accelerated stability tests were performed to select the optimal capsaicin nanoemulsion. The formulation was visually evaluated for turbidity and phase separation, followed by

spectrophotometric measurements for percent transmittance at 600 nm (λ_{max}). [14]

First, the optimised nanoemulsions were centrifuged at 5000 rpm for 30 minutes at 25°C. After passing the centrifugation test, the samples were subjected to three consecutive heating-cooling cycles; the nanoemulsions were kept at 40°C for 48 hours, then at 25°C for the same period of time. Furthermore, three freeze-thaw cycles were carried out, with the nanoemulsion freezing at -21°C for two days and then thawing at 25°C for another two days. A long-term stability study was also carried out, with nanoemulsions stored for six months at 25°C, 4°C, and 40°C. All experiments were performed in duplicate. [14]

CONCLUSION:

This review demonstrates the potential of various novel formulations in addressing diabetic neuropathy through enhanced drug delivery methods. Curcumin, when delivered via nano formulations, effectively reverses functional, sensorimotor and biochemical deficits in diabetic neuropathy by reducing neuroinflammation and boosting antioxidant defenses. This enhancement, which is more noticeable in the nanoformulated form, could lead to improved therapeutic results when treating diabetic complications. Similarly, nanoemulsions derived from *Morus Alba*'s phytoconstituent, chrysin, showed protective effects by reducing oxidative damage in alloxan-induced diabetic neuropathy in rats. The development of herbal ethosomal gels, capable of delivering active herbal extracts to the targeted skin site for extended periods with zero-order release, further enhances treatment options for diabetic neuropathy. Finally, as compared to traditional gels, the capsaicin nanoemulgel formulation, which was tailored for transdermal delivery, demonstrated greater pain alleviation and greatly enhanced skin penetration. These results imply that these cutting-edge delivery methods may provide more focused and efficient therapies

for diabetic neuropathy, ultimately leading to better patient outcomes and adherence. Also, the characterization studies of formulations for diabetic neuropathy revealed essential insights into their properties. Globule size analysis indicates that optimal particle sizes enhance bioavailability and efficacy. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) exhibit stability and homogeneity, which are essential for therapeutic results. Additionally, advantageous surface features for better drug distribution are highlighted by field emission scanning electron microscopy (FESEM). Furthermore, the integrity and compatibility of excipients and active components are verified using Fourier transform infrared spectroscopy (FTIR). Overall, these studies validate the effectiveness of the formulations and emphasize the importance of thorough design and analysis, paving the way for future clinical evaluations and improved management of diabetic neuropathy.

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